REMARKS

Claims 25-43 are pending in this application.

Applicants have cancelled claims 22-24 herein without prejudice or disclaimer.

Claim 25 has been rewritten in independent form. Claims 26 and 38 have been amended so that they depend from claim 25, rather than from cancelled claim 22.

Claim 35 has been amended to clarify that the claimed nucleic acid hybridizes under high stringency conditions. This amendment does not incorporate new matter and support for the amendment may be found at page 30, lines 12-21 of the specification. Claim 36 has been amended to clarify what conditions may qualify as high stringency conditions. No new matter has been added by this amendment and support for this amendment may be found at page 30, lines 12-21 of the specification.

Claims 42 and 43 are newly added herein. New claims 42 and 43 do not encompass new matter and are supported at pages 59-62 of the specification.

Applicants respectfully request that the Examiner consider the following remarks in response to the Office Action.

Priority Determination:

Applicants note that no art has been cited against the pending claims. Accordingly, although Applicants disagree with the Examiner's priority determination, further arguments are irrelevant at this time.

Rejection under 35 U.S.C. § 112, first paragraph:

Written Description

The Examiner has rejected claims 22-26 and 37-41 under 35 U.S.C. § 112, first paragraph, alleging that they fail to satisfy the written description requirement because the claims contain subject matter which was not described in the specification in such a

way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. Specifically, first the Examiner alleges that the specification fails to describe a representative number of species encompassed by the claims. Next, the Examiner notes that although the claims were previously amended to include a function for the claimed polypeptide, this did not remedy the lack of a written description because the Examiner alleges that the specification does not set forth common structural features that play a role in the inhibition of proliferation of T-cell lymphocytes. The Examiner further alleges that the specification fails to disclose the amino acids in the hydrophobic core of the protein that are essential for proper folding.

Applicants respectfully disagree with the Examiner's statement that the written description requirement has not been satisfied. As the Examiner notes, the written description requirement requires that an applicant's specification convey with reasonable clarity to those skilled in the art, that as of the filing date sought, he or she was in possession of the invention. *Vas-Cath, Inc. v. Mahurkar,* 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). A written description of an invention involving a chemical genus requires a precise definition, such as by structure, formula . . . of the claimed subject matter ***sufficient to distinguish it from other materials***. *Univ. of Calif. v. Eli Lilly & Co.,* 43 USPQ2d 1398, 1405 (Fed. Cir. 1997) (emphasis added). Since one skilled in the art can distinguish a described formula from other formulas and therefore can ***identify many of the species*** that the claims encompass, a described formula is normally an adequate description of the claimed invention. *Id.* at 1406 (emphasis supplied). Moreover, as noted in the Guidelines for Examination of Patent Applications Under 35 U.S.C. § 112, first paragraph, "Written Description" Requirement ("the Guidelines"), there is a "***strong presumption***" that an adequate written description of the claimed invention is present when the application is filed and, consequently, rejection of an original claim for lack of written description "***should be rare.***" 66(4) *Fed. Reg.* 1099, 1105 (2001); *see also, In re Wertheim*, 191 USPQ 90, 97 (CCPA 1976). The Guidelines further state that "[t]he examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an

applicant's disclosure a description of the invention defined by the claims." 66(4) *Fed. Reg.* at 1107; 191 USPQ at 97, (emphasis supplied).

Compliance with the written description requirement does not require an applicant to describe exactly the subject matter claimed; rather, the description must clearly allow a person of ordinary skill in the art to recognize that he or she invented what is claimed. *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). The test is whether the originally filed specification reasonably conveys to a person having ordinary skill in the art that applicant had possession of the subject matter later claimed. *In re Kaslow*, 217 USPQ 1089 (Fed. Cir. 1991). Moreover, in order to have possession of members of a claimed genus, the specification ***need not*** describe all of the species that the genus encompasses. *Amgen Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991).

In view of the legal standard regarding the written description requirement under 35 U.S.C. § 112, first paragraph, in combination with the interpretation of the written description requirement by the United States Patent and Trademark Office as set forth in the Guidelines, Applicants respectfully submit that the instant specification satisfies the written description requirement because it would be clear to one of skill in the art that Applicants possessed the claimed subject matter at the time of filing the instant application.

The Examiner has alleged that the specification fails to disclose the amino acids in the hydrophobic core of the protein that are essential for proper folding. However, there is nothing in the Guidelines that would require a patentee claiming a novel genetic sequence to disclose the amino acids in the hydrophobic core of the encoded protein. Therefore, Applicants submit that this is an improper ground of rejection and request that it be withdrawn.

Moreover, Applicants have disclosed many structural features of the claimed sequences. For example, several structural features, such as the single open reading frame, the translation initiation site, the transmembrane domain and sequences typical of the arginase family of proteins are disclosed at lines 24-29 on page 109 of the specification. A

host of PRO361 features disclosed in Figure 32 describe the polypeptide in great detail. For example, some of the PRO361 features described are conserved structures forming different protein domains: signal sequences; the transmembrane domain; N-glycosylation sites; cAMP and cGMP-dependent protein kinase phosphorylation sites; a tyrosine kinase phosphorylation site; and N-myristoylation sites (Figure 32).

The analysis for determining whether the present specification provides written description support for the invention defined by claims 22-26 and 37-41 may be performed by numerous methods, several of which are described in the Guidelines and further exemplified in the Revised Interim Written Description Guidelines Training Materials ("Written Description Training Materials"), published on the USPTO website at http://www.uspto.gov/web/offices/pac/writtendesc.pdf. These Written Description Training Materials are designed to provide additional clarity to the Guidelines which are published in the Federal Register, Volume 66, No. 4, pages 1099-1111. In fact, as indicated in the USPTO press release of March 1, 2000 introducing the Written Description Examination Training Materials (Press Release #00-15), these training materials were promulgated by the USPTO and are:

> "designed to aid PTO's patent examiners in applying the interim written description and utility guidelines in a uniform and consistent manner to promote the issuance of high quality patents. The training materials will also assist patent applicants in responding to the PTO when utility or written description issues are raised during the examination of a patent application." (emphasis added)

With regard to claims 22-41, the present situation is analogous to Example 14 on pages 53-55 of the Written Description Training Materials (Appendix A). More specifically, in Example 14 on pages 53-55 of the enclosed Written Description Training Materials, a claim directed to a protein and variants thereof having 95% sequence identity, all of which share the same biological function, is analyzed for its compliance with the written description requirement of 35 U.S.C. § 112, first paragraph. The Written Description Training Materials conclude that such a claim satisfies the written description requirement of 35 U.S.C. § 112, first paragraph, when (1) a single protein sequence is actually reduced to practice, (2) procedures for making variants of that "reduced to practice" protein sequence are conventional in the art, and (3) an assay is described

identification of other proteins having the same biological activity. The reasoning provided by the USPTO in the Written Description Training Materials is that:

> "[t]here is actual reduction to practice of the single disclosed species. The specification indicates that the genus of proteins that must be variants of SEQ ID NO:...does not have substantial variation since all of the variants must possess the specified [biological function] and must have at least 95% identity to the reference sequence, SEQ ID NO:...The single species disclosed ***is representative of the genus*** because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:...which are capable of the specified [biological function]. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by members of the genus.....{As such], the disclosure meets the requirements of 35 U.S.C. § 112, first paragraph, as providing adequate written description for the claimed invention." (emphasis added).

Analogous to Example 14 of the Written Description Training Materials, the present specification discloses and actually reduces to practice a nucleic acid recited in claims 22-26 and 37-41 (*i.e.*, SEQ ID NO:31) as well as a polypeptide encoded by that nucleic acid (*i.e.*, SEQ ID NO:32). Moreover, the nucleic acid variants encompassed within claims 22-26 and 37-41 ***do not have substantial variation*** with SEQ ID NO:31 because (a) they share at least 95% or 99% sequence identity with SEQ ID NO:31 or the encoded polypeptide (SEQ ID NO:32) (Applicants note that methods for routinely determining nucleic acid and/or amino acid sequence identity are described in detail in the present specification at page 23, line 34 to page 29, line 2, *see also* pages 34-54), and (b) they share the biological function of encoding a polypeptide that is able to inhibit proliferation of stimulated T cells. (Applicants note that the specification describes in detail in Example 34 a routine assay that is useful for identifying nucleic acids encoding polypeptides having this biological function). As such, the nucleic acids encompassed within claims 22-26 and 37-41 all share substantial common structural features (*i.e.*,

95%, or 99% sequence identity) and substantial common functional features (*i.e.,* encoding a polypeptide that is able to inhibit proliferation of stimulated T cells). Moreover, the present specification also describes conventionally known methods used and known in the art for preparing a multitude of variants (see the present specification at page 59, line 13 to page 63, line 36).

Given the above, Applicants respectfully submit that currently pending claims 25-26 and 37-41 satisfy the written description requirement of 35 U.S.C. § 112, first paragraph because the specification provides "a precise definition, such as by structure, formula ... of the claimed subject matter *sufficient to distinguish it from other materials*" as required by the Federal Circuit in *Univ. of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997). Moreover, claims 25-26 are analogous to the claim found to satisfy the written description requirement in Example 14 of the enclosed Written Description Training Materials. As such, under the Guidelines and the examination training materials promulgated by the USPTO for ensuring consistent examination of written description compliance during prosecution of patent applications, the written description requirement of 35 U.S.C. § 112, first paragraph, is satisfied for claims 22-26, and 37-41. Therefore, Applicants respectfully request this ground of rejection be withdrawn.

Rejection under 35 U.S.C. § 101:

The Examiner rejected claims 22-41 for alleged lack of utility. Specifically, the Examiner asserted that the invention is not supported by either a specific and substantial asserted utility or a well established utility. The Examiner states that the ability of a protein to stimulate lymphocyte proliferation in a Mixed Lymphocyte Reaction ("MLR") assay does not support a specific and substantial utility because the ability is assayed in an artificial *in vitro* system and the specification does not provide for what specific conditions or for which specific diseases the claimed invention would predictably function.

Applicants respectfully disagree. As the Examiner noted, Example 34, found on page 141 of the application, describes a MLR assay in which PRO361 tested positive, demonstrating that PRO361 has utility as an inhibitor of the proliferation of stimulated T-lymphocytes.

MLR is a well-established *in vitro* assay for assessing the ability of a test compound to stimulate or suppress T cell proliferation, and consequently the immune response of an individual. In brief, in a MLR assay, an immune response is produced by mixing T cells from antigenically distinct individuals and allowing them to react with one another in cell culture. The MLR assay is described in standard textbooks, including, for example, *Current Protocols in Immunology*, unit 3.12; edited by J.E. Coligan, A.M. Kruisbeek, D.H. Marglies, E.M. Shevach, W. Strober, National Institutes of Health, published by John Wiley & Sons, Inc., which is referenced in Example 34 on page 141 of the specification. The entire content of the *Current Protocols in Immunology* reference is expressly incorporated by reference into the disclosure of the present application.

MLR has been extensively used and is considered to be the best *in vitro* model available to study graft-versus-host disease and graft rejection. It is well known that the transplantation of tissues or organs between individuals with MHC incompatibilities quickly activates the recipient's immune system which then attempts to destroy the transplanted tissue or organ. Transplantation across minor histocompatibility loci generally induces a slower response. Physicians analyze the major and minor histocompatibility differences to predict the success of the graft and to adjust the aggressiveness of immunosuppressive therapy. MLR can be monitored qualitatively, for example, by following the incorporation of tritiated thymidine during DNA synthesis, by observing blast formation or by similar methods known in the art.

Inhibitors of MLR find utility in suppressing unwanted immune responses, which might, for example, result in graft rejection. For example, the ability of tepoalin, an immunomodulatory compound, to suppress graft-versus-host reaction, has been demonstrated in a MLR assay (Fung-Leung *et al., Transplantation* 60:362-8 (1995)) (*See* Appendix A).

Other immunosuppressants have also been routinely identified by MLR. For example, the specification, on page 141, discusses the inhibitory activity of PRO361 (with regard to T cell proliferation), as demonstrated in a MLR assay. At lines 8-9 of page 141, the

specification sets forth how PRO361 may be used, based on its function: "[c]ompounds which inhibit proliferation of lymphocytes are useful therapeutically where suppression of an immune response is beneficial." Accordingly, PRO361 polypeptides or their agonists are useful candidates for suppressing harmful immune response, *e.g.,* in the case of graft rejection or graft-versus-host disease. Similarly, inhibitors (antagonists) of PRO361 find utility in stimulating T-cell response, *e.g.* in the case of leukemia, and other types of cancer, and in immunocompromised patients, such as AIDS sufferers.

Rejection under 35 U.S.C. § 112, first paragraph:

Enablement

The Examiner contends that because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention.

Applicants respectfully disagree. As discussed above, the claimed nucleic acid has the specific, substantial, and credible utility of encoding a polypeptide which inhibits the proliferation of stimulated T-lymphocytes as demonstrated in the MLR assay experiment discussed in Example 34 at page 141 of the application.

Applicants respectfully request the Examiner reconsider and withdraw the rejection of claims 22-41 under 35 U.S.C. § 112 ¶1 for alleged inadequate disclosure on how to use the claimed invention.

The Examiner also rejects claims 22-41 for lack of enablement, based on an analysis of the *Wands* factors. Applicants respectfully disagree with the Examiner's analysis and conclusion.

The first *Wands* factor analyzed is the nature of the invention. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The claimed invention is a nucleic acid having at least 95% sequence identity to SEQ ID NO: 82 or 83, which encodes a polypeptide capable of inhibiting proliferation of stimulated T-lymphocytes.

The second *Wands* factor is the state of the prior art. The Examiner contends that the state of the prior art regarding the ability of a protein to inhibit the MLR assay is unpredictable and uncertain, since it is an artificial *in vitro* system and does not indicate for what specific conditions and for which specific diseases the protein would be useful. Applicants respectfully disagree. As discussed above, MLR is a well-established assay for assessing the ability of a test compound to stimulate or suppress T cell proliferation. It is described in standard textbooks, including *Current Protocols in Immunology*. Page 53 of *Current Protocols in Immunology* describes using a MLR assay to determine the presence of various MHC alleles. This information can then be used in assessing the success of a graft and in adjusting aggressiveness of immunosuppressive therapy. One well-known advantage of a MLR assay is that it gives a good indication of the degree of T-lymphocyte activation generated in response to MHC antigens of the potential graft. Thus, based on the results of this well-established assay, PRO361 predictably would be useful in treating graft-versus host disease, for example by assessing the success of a graft and adjusting aggressiveness of immunosuppressive therapy.

Wands requires the Examiner to consider the presence or absence of working examples. *Wands* 858 F.2d at 737. As the Examiner notes, Applicant's describe the working MLR assay example at page 141 of the specification.

The Examiner contends that there is no correlation taught or well known in the art between the MLR assay and *in vivo* treatment of diseases involving the immune response. Applicants respectfully disagree. As mentioned above, the ability of tepoalin, an immunomodulatory compound, to suppress graft-versus-host- disease was demonstrated *in vivo* as well as in a MLR assay. *See* Fung-Leung *et al.*, *Transplantation* 60:362-8 (1995) (Appendix A).

Finally, the Examiner asserts that there is no guidance in the specification regarding, for example, how patients would be treated with the disclosed polynucleotides or how the compounds would be administered. The claims, however, do not require that the polynucleotide be used to treat a patient. One of skill in the art will know how to use the disclosed polynucleotides in connection with the MLR assay. The results of the assay

alone provide one of skill in the art with valuable information to use in treating graft versus host disease, such as by enabling one skilled in the art to predict the success of a graft and adjust the aggressiveness of immunosuppressive therapy.

The *Wands* factors are analyzed as a tool to determine whether undue experimentation is required to practice a claimed invention. However, as the Federal Circuit has stated that:

> [t]he determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art (citations omitted). The test is not merely quantitative, since a *considerable amount of experimentation is permissible,* if it is merely routine, or *if the specification provides a reasonable amount of guidance* with respect to the direction in which the experimentation should proceed. *See In re Wands,* 858 F.2d 731, 737 (Fed. Cir. 1988).

Given the established utility of a MLR assay, the level of skill in the art, and the significant disclosure found in the specification, any experimentation that might be required to practice the claimed invention would be routine and not undue. Therefore, Applicants submit that the present invention is enabled by the specification and respectfully request that the Examiner withdraw this ground of rejection.

CONCLUSION

Applicants believe this Amendment and Request for Reconsideration fully responds to the Office Action. Applicants respectfully request the Examiner grant early allowance of this application. The Examiner is invited to contact the undersigned attorney for the Applicant via telephone if such communication would expedite this application.

Applicants believe no fee is due in connection with the filing of this Amendment, however, should any fees be deemed necessary for any reason relating to this paper, the Commissioner is hereby authorized to deduct said fees from Brinks Hofer Gilson & Lione Deposit Account No. 23-1925. A duplicate copy of this document is enclosed.

Respectfully submitted,

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